EXHIBIT B

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED, TAKEDA PHARMACEUTICALS NORTH AMERICA, INC., TAKEDA PHARMACEUTICALS LLC, TAKEDA PHARMACEUTICALS AMERICA, INC., and ETHYPHARM, S.A., Plaintiffs and Counterclaim-Defendants, v. MYLAN PHARMACEUTICALS INC., Defendant and Counterclaim-Plaintiff.	:	Civil Action No. 3:11-CV-02506-JAP-TJB **SECOND SUPPLEMENTAL DECLARATION OF DR. STEPHEN R. BYRN**

I, Stephen R. Byrn, under penalty of perjury, declare as follows:

1. My qualifications, prior testimony, and compensation can be found in my Declaration, dated March 23, 2012, and my Supplemental Declaration, dated April 18, 2012, which I incorporate herein by reference.

2. In addition to the materials referenced in my Supplemental Declaration, I have also considered (1) the transcript from my June 8, 2012 deposition; (2) the transcript from Dr. Mumper's June 6, 2012 deposition; (3) Mylan's Responsive Claim Construction brief, dated June 22, 2012; and (4) Dr. Mumper's Supplemental Declaration, dated June 22, 2012.

I. "permits to obtain reduced pH influence in the digestive tract" ('632 patent)

3. I disagree with Dr. Mumper's assertion that the phrase "permits to obtain reduced pH influence in the digestive tract" is indefinite.

4. As I explained in my March 23, 2012 Declaration, a person of skill in the art would understand this phrase to mean that "the active ingredient in the tablet is less influenced by stomach pH (*i.e.*, the drug is coated)." In other words, the limitation describes a characteristic of the tablet – that the tablet contains coated drug granules to protect the drug (*i.e.*, reduce the influence) from the acidic pH of the stomach. This limitation does not require any measurement of pH.

5. Thus, Dr. Mumper's assertion that a person of skill in the art would need to know the starting point and ending point of the influence of pH to the granule is incorrect. (Mumper Supp. Decl. ¶51.) The same holds true for Dr. Mumper's arguments regarding the particular influence on the pH (*i.e.*, increase, decrease, neutral) and the specific place within the digestive tract that the pH effect takes place. (Mumper Supp. Decl. ¶52.)

6. If there were any question about whether a particular tablet had "reduced influence of pH in the digestive tract," it would be routine for a person of skill in the art to expose coated particles to simulated gastric fluid and assess the stability of the active ingredient with a standard U.S. Pharmacopeia ("USP") assay.

II. "permits to obtain . . . reduced influence of viscosity" ('632 patent)

7. I also disagree with Dr. Mumper's assertion that the phrase "permits to obtain . . . reduced influence of viscosity" is indefinite.

8. As I explained in my March 23, 2012 Declaration, a person of skill in the art would understand this phrase to mean "the formulation influences viscosity less than the prior art formulations of record that have excipients increasing viscosity." I understand that the Court agreed with this construction in the *Zydus* litigation.

9. The "prior art formulations" in Plaintiffs' (and the Court's) construction refer to tablets designed to be dropped into a glass of liquid (such as water) to form a suspension that the patient drinks. To generate this suspension, the prior art formulations contain excipients that increase the viscosity of the liquid so that the microgranules containing the drug do not sink to the bottom of the glass, which could lead to the patient consuming less than the full intended dose of the drug.

10. At his deposition, Dr. Mumper acknowledged that the phrase "permits to obtain . . . reduced influence of viscosity" was included during prosecution to specifically distinguish the '632 invention from the above-described prior art formulations:

> Q. In rendering your opinion as to the purported indefiniteness of permits to obtain reduced influence of viscosity, did you take the prosecution history into account?
>
> A. Yes, I recall in the prosecution history that this claim term was included to differentiate the '632 claim from prior art . . . that included an excipient that increased the viscosity.

(***Ex. 34***, Mumper Dep. Tr. 110:12-21.)

* * *

> A. As I mentioned, I did look at the prosecution history and the prior art that included an agent that increased viscosity and looked at what that taught and what it was doing. I looked at the prosecution history. I understood that '632, claim 1 was trying to move around that prior art by having the term "reduced influence of viscosity."

(***Ex. 34***, Mumper Dep. Tr. 113:18-25.)

11. Dr. Mumper argues that a person of ordinary skill in the art would not be able to discern the meaning of this phrase because "it remains unknown as to 'who' or 'what' is permitted 'to obtain reduced influence of viscosity'" and because "[t]here is no explanation in the specification or file history as to whether it is the viscosity of the excipients that is reduced, the viscosity of the disintegrated tablet, or the viscosity of fluids in the digestive tract." (Mumper Supp. Decl. ¶56.) I disagree.

12. The prosecution history makes clear that the limitation relates to a formulation that influences the <u>viscosity of liquid</u> (such as water in a glass) less than prior art formulations containing excipients that increase the viscosity of such liquid in order to create a drug suspension. Thus, it would be clear to a person of skill in the art that there is no need to determine "who" is obtaining "reduced influence of viscosity." Moreover, the file history makes clear that the limitation pertains to the impact on the viscosity of the liquid (and not the "viscosity of the excipients, viscosity of the disintegrated tablet, or the viscosity of the fluids in the digestive tract," that Dr. Mumper refers to).

13. Dr. Mumper further argues that the '632 specification and file history fail to provide guidance as to how much excipient would be needed to have reduced influence of viscosity. (Mumper Supp. Decl. ¶55.)

14. A person of ordinary skill in the art, however, would know the types (and amounts) of excipients required to increase the viscosity of liquid in order to create a suspension like the prior art formulations discussed above; it follows that one of skill in the art would know what excipients to avoid in order to practice the invention. If there were any question as to whether a "formulation influences viscosity less than the prior art formulations of record that have excipients increasing viscosity," it would also be routine for a person of skill in the art to make viscosity measurements in accordance with the USP.

III. "enteric coating layer" ('994 patent)

15. Mylan and Dr. Mumper argue that I admitted the claimed enteric coating layer must be a blend of an enteric coating agent and sustained-release agent. (Def.'s Resp. Br. at 15-16; Mumper Supp. Decl. ¶¶35-36.) Mylan and Dr. Mumper mischaracterize my Declaration (at ¶20) and deposition testimony.

16. Nowhere in my declaration did I state that the enteric coating layer is limited to a blend or an admixture of an enteric coating agent and sustained-release agent. In fact, I made clear numerous times during my deposition that the enteric coating layer was not limited to such a blend or admixture:

> Q. That's right. You did. In fact, Dr. Shimizu revolved [sic] that problem, recognizing that if you add – however you called it -- add a mixture of enteric coating agent or sustained release agent, that you will avoid those problems?
>
> A. I will just go with the claims. **The combination of coatings, two compositions, like are said in the claims, avoid the problems. So the claims say they don't require an admixture.** They just say – well, I should – that's – I just want to get this right – "coated by a first component which is an enteric coating agent and a second component which is a sustained release agent."

(***Ex. 35***, Byrn Dep. Tr. 252:17-253:10 (emphasis added).)

> Q. That's right. And then in all of the -- in the examples, the way he -- in the examples that he has laid out in the specification -- we went over this before – is that he essentially was able to combine the two ingredients together which, in his view, resolves the problems that you talked about earlier with respect to formulating an ODT?

Q. Right?

A. **Well, in the examples he used one method of doing the claim. But that doesn't mean that there aren't other methods, and the examples are not limiting.**

(***Ex. 35***, Byrn Dep. Tr. 253:17-254:9 (emphasis added).)

IV. "an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent" ('994 patent)

17. Dr. Mumper also argues that I admitted the "enteric coating agent" and "sustained-release agent" are different agents. (Mumper Supp. Decl. ¶¶27-34.) Dr. Mumper is wrong.

18. As I explained repeatedly during my deposition, my opinion is that the patent includes the possibility of the "enteric coating agent" and "sustained-release agent" being the same excipient:

Q. **So you are saying that the sustained release agent and the enteric coating agent can be the exact same ingredient?**

A. Well, I am just reading the patent where it says "methacrylate copolymers"' and it says – it says the "aqueous enteric" – I am on column nine, line 27. It says: "The aqueous enteric coating polymer agent is preferably a methacrylate copolymer. The sustained release agent is preferably a methacrylate copolymer."

Q. So my -- the answer to my question is "yes," that's your position?

A. **Right, I think it's consistent with the patent, also.**

(***Ex. 35***, Byrn Dep. Tr. 75:16-76:9 (emphasis added).)

19. It is well-known in the pharmaceutical art that excipients often have multiple functions depending on the context in which the excipient is used. I explained this during my deposition:

A. You seem to be saying that, if something is an enteric coating agent, it can't be anything else, and vice versa. And there are lots of excipients that have multiple functions. So I'm not sure you can say that. You have to look at the system.

(***Ex. 35***, Byrn Dep. Tr. 126:10-15 (emphasis added).)

> Q. So first ingredient – so first component, second component, under your definition, could be the exact same ingredient. I just want to understand your position. Yes or no?
>
> * * *
>
> A. That there – I wouldn't rule out that they – **I wouldn't say that they could not be. They can be the exact same ingredient, but they may be processed – I just have to look at the context.**

(***Ex. 35***, Byrn Dep. Tr. 74:4-19 (emphasis added).)

20. Dr. Mumper asserts that I have not provided any example of a methacrylate copolymer that the pharmaceutical art references as both an enteric coating agent and a sustained-release agent. (Mumper Supp. Decl. ¶¶29.) He is wrong. I cited to two references in my March 23, 2010 Declaration that refer to Eudragit L30D-55 – the Eudragit agent that Dr. Mumper contends can only be an enteric coating agent – as a sustained-release agent.

> **Additional sustained release dosage forms of the present invention may be composed of the acrylate and methacrylate copolymers** available under the trade "Eudragit" from Rohm Pharma (Germany). . . . Preferred acrylate copolymers are copolymers of methacrylic acid and methyl methacrylate, such as the Eudragit L and Eudragit S series polymers. **Particularly preferred** such copolymers **are Eudragit L-30D-55** and Eudragit L-100-55 (the latter copolymer is a spray-dried form of Eudragit L-30D-55 that can be reconstituted with water). (***Ex. 8***, US 2009/0304789, p. 5 (emphasis added).)

> **Eudragit L30D-55 has been used for decades as a matrix former in sustained-release tablets** due to its excellent binding properties and the retardation effects it provides. (***Ex. 12***, Diego G. Alvarez et al., *Drug-Release Mechanisms*, DRUG DELIVERY TECH., July/Aug. 2007, at 30 (emphasis added).)

21. Dr. Mumper argues that the teachings of these two references are irrelevant because they do not relate to the teachings of the '994 patent. (Mumper Supp. Decl. ¶¶29.) But Dr. Mumper concedes that whether the "sustained-release agent" actually functions as a sustained-release agent does not matter, and that the claim only requires the presence of both an enteric coating agent and a sustained-release agent as those terms are known in the art. (Mumper Supp. Decl. at ¶30.) Thus, the two references are directly on point, since they reflect the fact that

Eudragit L30D-55 is known in the art as a sustained-release agent (in addition to an enteric coating agent).

V. "fine granules having an average particle diameter of 400 µm or less" ('994 patent)

22. Over the years, FDA has set strict requirements as to particle size for many drug substances; in many cases, particle size determines dissolution rate, and dissolution rate determines absorption and bioavailability.

23. Since in and about 1980, I have had extensive experience with particle size testing. Almost from their first introduction in the 1980s, I worked with laser diffraction instruments. SSCI, a company I co-founded, relied on a laser diffraction instrument of similar construction and operation to the Sympatec HELOS RODOS instrument disclosed in the '994 patent.

24. Since 1990, I have taught courses on Pharmaceutical Solids that incorporate lectures on particle size testing. Even today, I continue to lecture on particle size in Purdue's Pharmaceutical Solids course, SSCI courses, and in Purdue's Master's Degree Program in regulatory and quality compliance (that I cofounded).

25. I worked with the USP from 1990-2005. I chaired the PQRI Drug Substance Technical Committee from 1997-2001, which commissioned and oversaw the work that culminated in the Snorek paper.

26. Thus, in the various capacities described above and as outlined in my prior Declarations and curriculum vitae, I have gained extensive knowledge about the error implicit in particle size testing – whether with laser diffraction instruments or other particle size instruments.

27. I understand that, based on my testimony that the known standard of error was much larger than 10% prior to 1999, Mylan and Dr. Mumper argue that I somehow conceded there was no universally accepted deviation for laser diffraction in the 1998-1999 timeframe. (Def.'s Resp. Br. at 6-8; Mumper Supp. Decl. at ¶¶12-13.) They are wrong.

28. Because Mylan's questions relating to measurement error during my deposition were very open-ended as to time (*i.e.*, prior to 1999), my testimony captured my understanding of those skilled in the art from time periods well before 1999 (*e.g.*, 1980's, early 1990s). My testimony was not specific to the 1998-1999 timeframe, because the questions were not so limited.

29. Indeed, I made clear in my deposition that the 10% standard of error disclosed in the USP and the Snorek paper is reflective of the general understanding that a person of ordinary skill in the art had during the relevant 1998-1999 time period. (***Ex. 35***, Byrn Dep. Tr. 179:10-16 ("Although they couldn't go to [the USP or Snorek], they would come out with the same analysis . . . my opinion is that 10 percent is a conservative number based on all of my analysis. I think that's what a person skilled in the art would come up with.").) As explained above, I chaired the PQRI Drug Substance Technical Committee, when it commissioned and discussed the work culminating in the Snorek paper, from 1997-2001. Thus, the general understanding of those skilled in the art during the 1998-1999 timeframe was that a 10% standard of error applied to particle size measurements with laser diffraction.

30. Dr. Mumper asserts that "to understand the standard deviation for laser diffraction, a person of ordinary skill in the art would look to the specifications for the particular machine being used." (Mumper Supp. Decl. at ¶16.) Based on such specifications, Dr. Mumper argues that the known error for the HELOS RODOS laser diffraction instrument during the

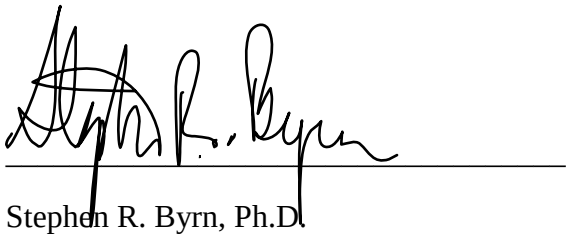
relevant timeframe ranged from about 0.4% to 1.0%, not 10%. (Mumper Supp. Decl. ¶17.) I do not agree. As I testified in my deposition, there are multiple types of errors. The error Dr. Mumper references is instrument error, which involves measuring the same sample over and over again. In my opinion, a person of skill in the art would find instrument error irrelevant to the type of particle size measurements necessitated by the '994 patent. (***Ex. 32***, Byrn Dep. Tr. 163:5-165:4, 175:16-176:7.)

31. A person of ordinary skill in the art considering the '994 patent would understand that the "average particle diameter" limitation refers to measurements of fine granules from a pharmaceutical batch. Thus, one of skill in the art would want to know whether the fine granules for a particular pharmaceutical batch fall within the scope of the claim. In the 1998-1999 timeframe, a person of skill in the art assessing average particle size would have performed a partial Method Validation study, similar to that subsequently described in the Snorek paper or in the USP. (***Ex. 32***, Byrn Dep. Tr. 163:5-165:4, 175:16-176:7.) Such a study involves obtaining representative samples from the same batch; a person of skill in the art in the 1998-99 timeframe would know that +/- 10% is a conservative standard of error for such measurements. As I stated in my deposition, in the 1998-99 timeframe, FDA required particle size specifications, and persons of skill in the art were both defining and exchanging particle size specifications; these particle size specifications reflected the error subsequently captured by the Snorek paper and in the USP. (***Ex. 35***, Byrn Dep. Tr. 166:13-21.)

32. Dr. Mumper further asserts that it would be unreasonable to assume a 10% deviation for all particle size measurement methods because other methods for measuring particle size, such as sieving and sedimentation, would have been more precise than a 10% standard deviation as of the filing date of the '994 patent. (Mumper Supp. Decl. ¶21.) I disagree.

As explained in my deposition, during the timeframe of 1998-1999, the error for both sieving and sedimentation involved greater error than laser diffraction. (***Ex. 35***, Byrn Dep. Tr. 183:8-184:15.) Because laser diffraction was known to be a precise method of measuring particle size, a person of skill in the art would have understood a 10% standard of error to be a conservative figure that can apply to other particle size measurement methods. (***Ex. 32***, Byrn Dep. Tr. 159:5-20.)

Date: July 6, 2012



Stephen R. Byrn, Ph.D.